



PATENT  
0459-0490P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant: Lorenzo WILLIAMS Conf.: 8775

Appl. No.: 09/680,471 Group: 1743

Filed: October 6, 2000 Examiner: Yelena GAKH

For: A METHOD FOR SYNTHESIS, SEPARATION AND  
SCREENING OF A PLURALITY OF COMPOUNDS  
IN THE SAME BULK OF A STATIONARY PHASE  
(as amended)

L E T T E R

Assistant Commissioner for Patents  
Washington, DC 20231

May 10, 2002

Sir:

Under the provisions of 35 U.S.C. § 119 and 37 C.F.R. § 1.55(a), the applicant hereby claims the right of priority based on the following application:

<u>Country</u>	<u>Application No.</u>	<u>Filed</u>
NORWAY	1999 4873	October 6, 1999

A certified copy of the above-noted application is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fee required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By: *Gerald M. Murphy Jr.*  
Gerald M. Murphy, Jr., #28,977

P.O. Box 747  
Falls Church, VA 22040-0747  
(703) 205-8000

*KJR*  
GMM/KJR/bsh

Attachment



# KONGERIKET NORGE

The Kingdom of Norway



Lorenzo Williams  
09/680,431  
October 6, 2000  
0459-0490P  
BIRCH, STEWART,  
KOLASCH & BIRCH, LLP  
(703) 205-8000

## Bekreftelse på patentsøknad nr

*Certification of patent application no*

**1999 4873**

**TC 1700**

MAY 16 2002

**RECEIVED**

Det bekreftes herved at vedheftede dokument er nøyaktig utskrift/kopi av ovennevnte søknad, som opprinnelig inngitt 1999.10.06

*It is hereby certified that the annexed document is a true copy of the above-mentioned application, as originally filed on 1999.10.06*

2001.01.09

*Freddy Strømmen*

Freddy Strømmen  
Seksjonsleder

*Ellen B. Olsen*

Ellen B. Olsen



**PATENTSTYRET**  
Styret for det industrielle rettsvern

1c  
PATENTSTYRET

KR/HBS/101210  
99/10/06

06.0KT99 994873

**Patentsøknad nr.:**

**Patentsøker:** SINVENT AS

**Tittel:** A Combined Technology for the Synthesis, Separation,  
Screening and Analysis of a Combinatorial Library

## Introduction

The present invention relates to a system and method for performing synthesis, separation, analysis and screening of chemical entities. Especially, the invention concerns a combined technology for the synthesis, separation, screening and analysis of a combinatorial library. The invention also concerns uses of the system and method.

## Background of the Invention

Presently there are no known methods that combine the four key areas of synthesis, separation, analysis and screening. Other technologies which have partial accomplishments in these areas are based on solid phase parallel/combinatorial synthesis whereby synthesis, separation and sometimes, but rarely, analysis or biological evaluation are performed (see for example "Combinatorial Chemistry: Synthesis and Application" eds. S.R. Wilson and A.W. Czarnik, John Wiley & Sons Inc., NY, 1997). These methods require attachment and sometimes cleavage reactions to and from a support. The normal scope of synthetic chemistry maybe somewhat restricted here, since most reactions are developed in solution. Purification is usually achieved by sequentially washing the resin or solid support. Biological testing has been performed on compounds still attached to solid supports, though it is unknown as to how this effects the results of these assays. Solution chemistry has been used to try and overcome some of the disadvantages above. However, methods for purification can often be complex, requiring the use of sequestering reagents, extractions, column chromatography, etc. In both solution and in the solid phase it is critical that the chemistry is optimised. This can often be a very time consuming process. Today's technology is often very complex and time consuming and expensive equipment is usually necessary to achieve the end-goal of screening new compounds. Bioautography encompasses both the separation of compounds from a mixture and their subsequent biological testing. This technique, to our knowledge, has not been combined with synthesis. It has largely been used in the identification and isolation of natural products. These compounds are then screened *in situ*.

## Summary of the Invention

It is an object of the present invention to provide a system and a method, which allows for the sequential and rapid synthesis, purification, analysis and testing or screening of chemical entities, and to combine these four key areas. It is also an object of the present invention to provide a methodology for both library synthesis and screening at high speed and low cost with minimal space requirements.

In accordance with a first aspect of the present invention, there is provided a system for performing a sequence of synthesis, separation, analysis and screening of chemical entities, comprising various means for executing said sequence, characterized in that the system comprises one medium for the performance in or on said medium of the synthesis, separation, analysis and screening sequence.

In accordance with a second aspect of the present invention there is provided a method for performing in sequence synthesis, separation, analysis and screening of chemical entities, characterized by performing synthesis, separation, analysis and screening in or on one and the same medium.

The medium may be a plate comprising a stationary support, which can be used for separation purposes, and a plate backing. The support may consist of silica gel, alumina, cellulose or other sorbent or inert material for chromatography. The plate may be attached to an inert support composed of paper, fibrous materials, glass, plastic or metal, preferably aluminium. The plate may preferably have a dimension of 10cm x 10cm and the thickness of the plate backing may preferably be in the range from 10 $\mu$ m to 2mm.

In another embodiment of the invention the plate preferably is a thin layer chromatography plate.

In another further embodiment of the invention the medium may also be a gel or solution.

To accelerate the synthesis the medium may be exposed to microwave radiation and separation may be performed by eluting at least once in at least one dimension with a suitable eluent or eluents, e.g. ethyl acetate-hexane, methanol-dichloromethane-ammonia, methanol-acetonitrile-ammonium phosphate or n-

butanol-pyridine-water-glacial acetic acid. Preferably, analysis is accomplished by a non-destructive method including but not restricted to using UV-light, densitometry with for example UV or IR detection, Raman spectroscopy, electrochemical detection and or mass spectrometry, e.g. MALDI (Matrix Assisted Laser Desorption Ionisation), SALDI (Surface Assisted Laser Desorption Ionisation). Screening may be performed with biological or chemical screening methods, like bioautographic techniques, overlay techniques, immunostaining, autoradiographic screening, enzymatic analysis or derivatisation. However, screening is also possible via binding studies or complexation studies.

The invention also comprises uses of the system as stated above and the method as stated above for the synthesis of compounds and derivatives thereof to discover or optimise lead compounds especially for biological evaluation, reaction optimisation, the synthesis of a combinatorial library, and then especially a library of arylpiperazines, sulfonamides, amino acids, amides, alcohols and amino alcohols, aldehydes and amino aldehydes, or products derived from a multi-component reaction. Other uses of the system as stated above and the method as stated above comprise synthesis of catalysts, derivatisation of compounds, e.g. natural products, identification of unknown compounds or natural products and metabolites thereof, identification of compounds obtained from fermentation extracts/processes or unknown compounds from other sources, for the detection or synthesis of biologically important compounds, for the synthesis or derivatisation of agrochemicals, e.g. pesticides or herbicides, and for reaction optimisation, especially with the assistance of microwave radiation. Further uses include the analysis of organic or inorganic anions together with metal cations, e.g.  $\text{Ni}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Co}^{2+}$ ,  $\text{Fe}^{2+}$ ,  $\text{Fe}^{3+}$ , analysis of toxic anions, e.g. arsenate, arsenite, azide and cyanide, analysis of organic or inorganic cations, e.g. alkylamines, alkali metal ions and alkaline-earth metal ions, the analysis of common inorganic anions such as chloride, bromide, iodide, fluoride, sulfite and phosphate, the analysis of organic acids and biomolecules, like DNA, short oligonucleotides of DNA, RNA and antisense oligonucleotides, the development of chiral analytes and support materials for use in synthesis or separation technology, and for the detection of drugs, e.g. narcotics, analgesics, CNS stimulants, tranquillisers, etc.

The technique described enables a rapid route from synthesis to the testing of chemical compounds. The chemistry does not need to be optimised and vital information can also be gained by the testing of by-products/reagents simultaneously if desired. Screens can be performed without need for reaction work-up. These 4 steps/key areas can be performed on the same medium without the need for undesired chemical manipulations, or further handling. Each of these four processes is in the present invention performed step-wise on the same medium.

10 **Brief Description of the Drawings**

The objects and features of the present invention, which are believed to be novel, are set forth with particularity in the appended claims. The present invention together with further objects and advantages, may best be understood by reference to the following description, taken in connection with the accompanying drawings, in which:

Figure 1 shows a view of a medium according to one embodiment of the invention for the sequential synthesis, purification, analysis and screening, and

Figure 2 shows a sequence for the synthesis, separation, analysis and testing of compounds on the same medium according to an embodiment of the invention.

20 **Description of the Preferred Embodiments**

The medium according to an embodiment of the present invention comprises a plate 1 containing a stationary support 2, which can be used for separation purposes, and a plate backing 3. The plate is shown in Figure 1. The size and shape of the plate 1 is important only in terms of resolution. A 10 cm x 10 cm plate is often adequate for most purposes. Larger plates, e.g. 20 cm x 20 cm allow for at least 40 different parallel runs to be performed. The technique can be performed on media independent of shape, though variations in the mode of separation may be required; e.g. radial chromatography is necessary with a circular medium. The plate backing 3 may be composed of glass, plastic, aluminium or other suitable inert material, like paper and fibrous materials, and the

support may consist of silica gel, alumina, cellulose, other sorbent or inert material for chromatography or other such media as described in "Thin-Layer"

Chromatography" by B. Fried and J. Sherma (4<sup>th</sup> ed., Chromatographic Science Series Volume 81, Marcel Dekker, Inc., New York, 1999, viii + 499pp.). The

thickness of the support may vary from tens of micrometers to several millimetres.

Synthesis can be performed either in the normal synthetic manner in solution, or directly on the plate. If performed in the normal manner small aliquots of the reaction medium (not worked-up) may be placed onto the plate either manually or using automation, e.g. by use of a liquid handler. Reactions that take place directly on the plate may occur either in solution, especially if solvent is used to apply the reagents, or in the solid phase. Reactions that occur slowly directly on the plate 1 may be accelerated by treatment with microwave radiation providing that the support 2 absorbs the radiation. Many different reactions can be performed in a parallel fashion on the plate, the limiting factor being resolution. A loss in resolution is noticeable if the plate is overloaded either with a sample or with the number of samples that are in close proximity to each other.

Figure 2 shows the combination of synthesis, separation, analysis and testing of compounds on a plate 1. After synthesis the chemical entities are separated by elution, then subjected to on-plate analysis and eventually screened.

In Figure 2 the spot B1 exhibits the most activity in the screen.

After synthesis (which may or may not be complete) the materials are separated from each other by elution with a suitable eluent, where the eluent may consist of one or a mixture of a number of solvents and other auxiliary agents, e.g. ethyl acetate-hexane, methanol-dichloromethane-ammonia, methanol-acetonitrile-ammonium phosphate, n-butanol-pyridine-water-glacial acetic acid, etc. Elution is not restricted to just one dimension, and may also be performed several times for each dimension. A mixture or a number of reactions may be separated in a two dimensional manner by first eluting in one direction, drying the plate and rotating it 90 degrees, and then by eluting it in another. Undesired areas or regions may be transferred or grafted onto another medium, e.g. filter paper, whilst the plate is still saturated with solvent. This can be achieved by pressing the other medium on top of the plate. Screening can then be performed directly on the plate.

After evaporation of solvent the compounds, reagents and starting materials can be visualised in a number of ways. Chromogenic methods where the spots are stained usually by derivatisation can be used as described in "Thin-Layer Chromatography" by B. Fried and J. Sherma (4<sup>th</sup> ed., Chromatographic Science Series Volume 81, Marcel Dekker, Inc., New York, 1999, viii + 499pp.). Non-destructive methods include use of ultra-violet light providing the compounds contain a chromophore, and densitometry with either ultra-violet or infra-red detection. Densitometry is advantageous since it can be used for quantification purposes. MALDI or SALDI mass spectrometry may also be used on the surface of the plate for characterisation purposes. The analysis also allows for quantification if necessary, e.g. by use of a densitometer or Flame Ionisation Detector (FID). Quantification is largely problematic in combinatorial and parallel synthesis. Signal producing systems such as radio labelling, an enzyme label or fluorophore can however also be used.

Separation may also be performed by using electrophoretic techniques. For example capillary gel electrophoresis may be used for the size-based separation of biological macromolecules such as oligonucleotides, DNA restriction fragments and proteins. Densitometry, other scanning devices and mass spectrometry may be used for detection purposes.

Screening on the plate can be performed in the traditional manner, e.g. as with bioautographic techniques, autoradiographic screening, immunoassay or enzyme inhibition techniques.

Zones of activity or inactivity can be detected and this information used for further study. The screening may involve looking for an optimal property in the library either by analytical methods or by physical methods that may require further interaction of the compounds in the library. Other forms of screening may be performed as described in "Combinatorial Chemistry: Synthesis and Application" eds. S.R. Wilson and A.W. Czarnik, John Wiley & Sons Inc., NY, 1997.

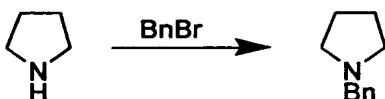
The system and method described above have a wide range of uses as stated earlier in the description, and examples of experiments performed will be given below.

In the following examples, the present invention will be elucidated in more detail. The examples are not meant to be limiting to the invention, but serve only as examples of experiments where synthesis, purification, analysis and biological testing have been performed sequentially on the same medium.

## EXAMPLE 1

### A. Synthesis

Pyrrolidine (5 µl, 0.06 mmol) was applied as a single spot to a TLC plate (0.25 mm thick, Silica gel 60F254). Benzyl bromide (5 µl, 0.04 mmol) was then applied to the same area. In another experiment the reactants were applied to the plate in solution, e.g. as 0.1 M solutions in dichloromethane, and the solvent allowed to evaporate from the plate. The scheme below shows the reaction between pyrrolidine and benzyl bromide.



### B. Separation

The TLC plate was eluted with 10 % MeOH-CH<sub>2</sub>Cl<sub>2</sub>. The solvent was then allowed to evaporate from the plate. Spots were visualised in a non-destructive manner with ultra-violet light of wavelength 254 nm. Spots could also be visualised in a destructive fashion by derivatisation if necessary, e.g. by use of a ninhydrin staining reagent on a duplicate plate, and the product areas cross-correlated.

### C. Analysis

Product spots could be analysed directly on the plate by mass spectrometry. In addition the spots from a duplicate plate were analysed by first scraping the desired areas from the plate and by dissolving the substrates in a suitable solvent and filtering off the product. Routine analysis could then be performed by, e.g. NMR, GCMS, etc.

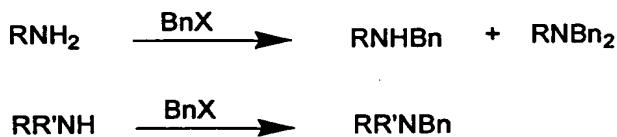
#### D. Screening

An agar gel containing the bacterium *Serracia marcescens* was poured over the TLC plate at 40 °C. The red coloured gel was allowed to cool and the plate left overnight at room temperature. The following day white inhibition zones were clearly visible around the product, indicating that the product had antibacterial activity against this strain. Unreacted benzyl bromide also showed some activity against this strain.

#### 10 EXAMPLE 2

##### **Synthesis in Parallel**

A library of secondary and tertiary amines was synthesised in a parallel and similar fashion to that in Example 1. These were synthesised from primary and secondary amines by their reaction with benzyl bromide. The primary amines afforded a mixture of both secondary and tertiary amine products that could be screened simultaneously in the same assay. After synthesis the products were separated by elution as in Example 1 (analysis and screening were similarly performed as before). The reaction schemes are shown below.



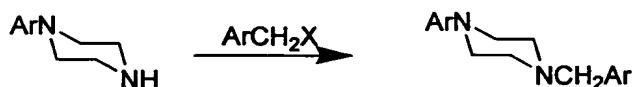
20

#### EXAMPLE 3

##### **Microwave Assisted Parallel Synthesis**

A library of piperazines was synthesised in a parallel and similar fashion to that in Example 1. These were synthesised from 1-arylpiperazines by their reaction with benzyl halide derivatives. Reactions were optimised in this case by use of microwave radiation. After application of reagents onto a glass-backed TLC plate (2mm thick, silica gel 60F254), the plate was placed in a domestic microwave oven. The plate was irradiated at about 1000 W for 5 min to facilitate

reaction. After cooling of the plate, the products were separated and screened as in Example 1 yielding products that showed growth inhibition of *Serracia* sp. The scheme below illustrates the reaction outlined in example 3.



#### **EXAMPLE 4**

##### **Microwave Assisted Parallel Synthesis**

A library of sulfonamides was synthesised in a parallel and similar fashion to that in Example 3. These were synthesised from 1-arylpiperazines by their reaction with aryl sulfonylhalide derivatives. Reactions were optimised in this case by use of microwave radiation. After application of reagents onto a glass-backed TLC plate, the plate was placed in a domestic microwave oven. The plate was irradiated at about 1000 W for 5 min. After cooling of the plate, the products were separated and screened as in Example 1. Excess sulfonylhalide was advantageously degraded to the corresponding sulfonic acid making analysis and screening easier. Several products showed activity against *Serracia* sp. The following scheme is representative of this type of reaction.



#### **EXAMPLE 5**

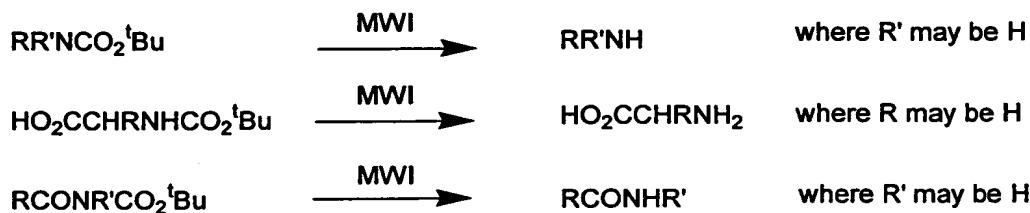
##### **Parallel Synthesis**

A library of mono and bisulfonamides was synthesised in a parallel and similar fashion to that in Example 2. These were synthesised from 1-arylpiperazines by their reaction with aryl bisulfonylhalide derivatives. The products were separated and screened as in Example 1. Several products showed growth inhibition of *Serracia* sp. The following scheme shows the synthesis of both mono and bisulfonamides.



**EXAMPLE 6****Deprotection**

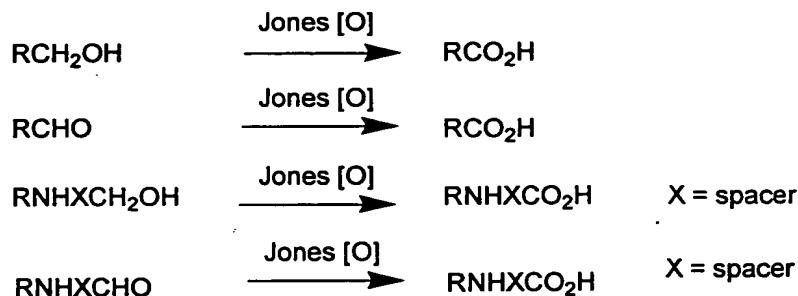
A library of N-Boc protected amines, amides and amino acids was deprotected in the following manner. After synthesis the substrates on a TLC plate were subjected to microwave radiation at 1000 W for 10 min in a domestic microwave oven to facilitate deprotection. The deprotected compounds were then separated on the plate (and can be screened as in Example 1). Typical deprotections are listed below.



10

**EXAMPLE 7****Oxidation**

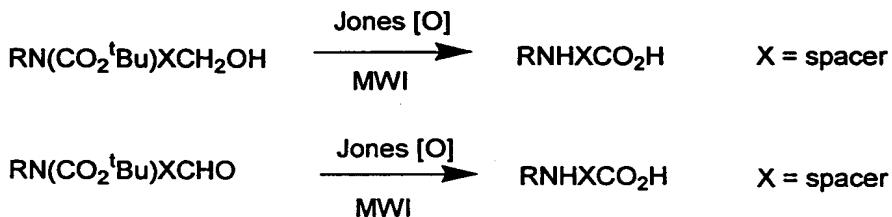
A library of alcohols, aldehydes, amino alcohols and amino aldehydes were oxidised with Jones reagent ( $\text{CrO}_3/\text{H}_2\text{SO}_4$ ). The substrates were applied to a TLC plate and excess Jones reagent applied. The TLC plate was then irradiated at 1000 W for 10 min in a domestic microwave oven to assist oxidation. The resultant carboxylic acids were then separated on the plate (and can be screened as in Example 1). Typical oxidations are listed below.



20

**EXAMPLE 8****Oxidation and Simultaneous D protection**

A library of N-Boc protected amino alcohols and amino aldehydes were simultaneously deprotected and oxidised with Jones reagent ( $\text{CrO}_3/\text{H}_2\text{SO}_4$ ). The substrates were applied to a TLC plate and excess Jones reagent applied. The TLC plate was then irradiated at 1000 W for 10 min in a domestic microwave oven to facilitate both oxidation and deprotection. The resultant deprotected amino acids were then separated on the plate (and can be screened as in Example 1).

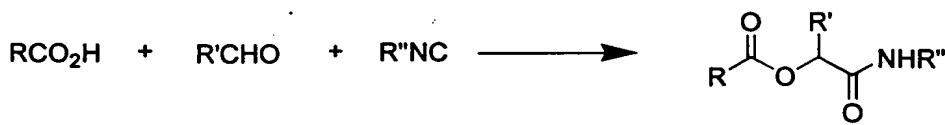


10

The simultaneous oxidation/deprotection schemes are shown below.

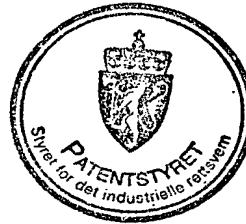
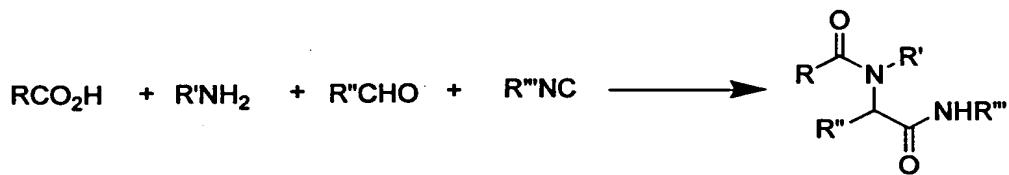
**15 EXAMPLE 9****Reactions in Solution: Multi-Component Reactions**

A library based on the Passerini reaction was synthesised in solution by reaction of various carboxylic acids with several aldehydes and isocyanides. The products were then separated as in Example 1 (similarly the product spots can be 20 screened as in Example 1.) The Passerini reaction is illustrated below.



**EXAMPLE 10****R actions in Solution: Multi-Component Reactions**

A library based on the Ugi reaction was synthesised in solution by reaction of various carboxylic acids with several aldehydes, amines and isocyanides. After separation the product spots were screened as in Example 1. The Ugi reaction is illustrated below.



**CLAIMS**

1. System for performing a sequence of synthesis, separation, analysis and screening of chemical entities, comprising various means for executing said sequence,  
characterized in that the system comprises one medium for the performance in or on said medium of the synthesis, separation, analysis and screening sequence.
- 10 2. System according to claim 1,  
characterized in that the medium is a plate comprising a stationary support, which can be used for separation purposes, and a plate backing.
- 15 3. System according to claim 2,  
characterized in that the support consists of silica gel, alumina, cellulose or other sorbent or inert material for chromatography, and that the plate backing is an inert support composed of glass, plastic or metal, preferably aluminium.
4. System according to claims 2 or 3,  
20 characterized in that the size of the plate is 10cm x 10cm and that the thickness of the plate backing is in the range from 10µm to 2mm.
5. System according to claim 1,  
characterized in that the medium is a thin layer chromatography plate.  
25
6. System according to claim 1,  
characterized in that the medium is a gel.
7. System according to claim 1,  
30 characterized in that the medium is a solution.

8. Method for performing in sequence synthesis, separation, analysis and screening of chemical entities,

characterized by performing synthesis, separation, analysis and screening in or on one and the same medium.

5

9. Method according to claim 8,

characterized by accelerating the synthesis by exposing the medium to microwave radiation.

10

10. Method according to claim 8,

characterized by separating components/reactants by eluting at least once in at least one dimension with a suitable eluent, e.g. ethyl acetate-hexane, methanol-dichloromethane-ammonia or n-butanol-pyridine-water-glacial acetic acid.

15

11. Method according to claim 8,

characterized by separating via electrophoresis.

12. Method according to claim 8,

20

characterized by analysing via a non-destructive method, e.g. by methods using UV-light, densitometry with UV or IR detection, Raman spectroscopy or mass spectrometry.

13. Method according to claim 8,

25

characterized by screening with biological or chemical screening methods, e.g. bioautographic techniques, overlay techniques, immunostaining, autoradiographic screening, enzymatic analysis or derivatisation.

14. Method according to claim 8,

30

characterized by screening via binding studies.

15. Method according to claim 8,  
characterized by screening via complexation studies.
16. Use of the system according to any of claims 1-7 and method according to  
any of claims 8-15 for the synthesis of compounds and derivatives thereof to  
discover or optimise lead compounds for biological evaluation.
17. Use of the system according to any of claims 1-7 and method according to  
any of claims 8-15 for the synthesis of a combinatorial library.
- 10
18. Use according to claim 17,  
characterized in that the combinatorial library is a library of  
arylpiperazines.
- 15
19. Use according to claim 17,  
characterized in that the combinatorial library is a library of sulfonamides.
- 20
20. Use according to claim 17,  
characterized in that the combinatorial library is a library of amino acids.
- 20
21. Use according to claim 17,  
characterized in that the combinatorial library is a library of amides.
- 25
22. Use according to claim 17,  
characterized in that the combinatorial library is a library of alcohols and  
amino alcohols.
- 30
23. Use according to claim 17,  
characterized in that the combinatorial library is a library of aldehydes  
and amino aldehydes.

24. Use according to claim 17,  
characterized in that the combinatorial library is a library of products  
derived from a multi-component reaction.
- 5 25. Use of the system according to any of claims 1-7 and method according to  
any of claims 8-15 for the synthesis of catalysts.
- 10 26. Use of the system according to any of claims 1-7 and method according to  
any of claims 8-15 for the identification of natural products and/or metabolites  
thereof, compounds obtained from fermentation extracts/processes or unknown  
compounds from other sources.
- 15 27. Use of the system according to any of claims 1-7 and method according to  
any of claims 8-15 for the derivatisation of compounds, e.g. natural products and  
or metabolites thereof.
- 20 28. Use of the system according to any of claims 1-7 and method according to  
any of claims 8-15 for the detection of drugs, e.g. narcotics, analgesics, CNS  
stimulants, and tranquillisers.
- 25 29. Use of the system according to any of claims 1-7 and method according to  
any of claims 8-15 for the detection or synthesis of biologically important  
compounds.
- 30 30. Use of the system according to any of claims 1-7 and method according to  
any of claims 8-15 for the synthesis of agrochemicals, e.g. pesticides or  
herbicides.
- 35 31. Use of the system according to any of claims 1-7 and method according to  
any of claims 8-15 for reaction optimisation.

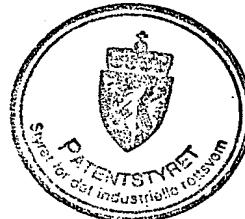
32. Use of the system according to any of claims 1-7 and method according to any of claims 8-15 for reaction optimisation with the assistance of microwave radiation.
- 5 33. Use of the system according to any of claims 1-7 and method according to any of claims 8-15 for the analysis of organic or inorganic anions together with metal cations, e.g.  $\text{Ni}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Co}^{2+}$ ,  $\text{Fe}^{2+}$ ,  $\text{Fe}^{3+}$ .
- 10 34. Use of the system according to any of claims 1-7 and method according to any of claims 8-15 for the analysis of toxic anions, e.g. arsenite, arsenite, azide, cyanide.
- 15 35. Use of the system according to any of claims 1-7 and method according to any of claims 8-15 for the analysis of common inorganic anions such as chloride, bromide, iodide, fluoride sulfite and phosphate.
- 20 36. Use of the system according to any of claims 1-7 and method according to any of claims 8-15 for the analysis of organic or inorganic cations, e.g. alkylamines, alkali metal ions, alkaline-earth metal ions.
37. Use of the system according to any of claims 1-7 and method according to any of claims 8-15 for the analysis of organic acids.
- 25 38. Use of the system according to any of claims 1-7 and method according to any of claims 8-15 for the development of chiral analytes.
39. Use of the system according to any of claims 1-7 and method according to any of claims 8-15 for the analysis of DNA.
- 30 40. Use of the system according to any of claims 1-7 and method according to any of claims 8-15 for the analysis of short oligonucleotides of DNA, RNA and antisense oligonucleotides.

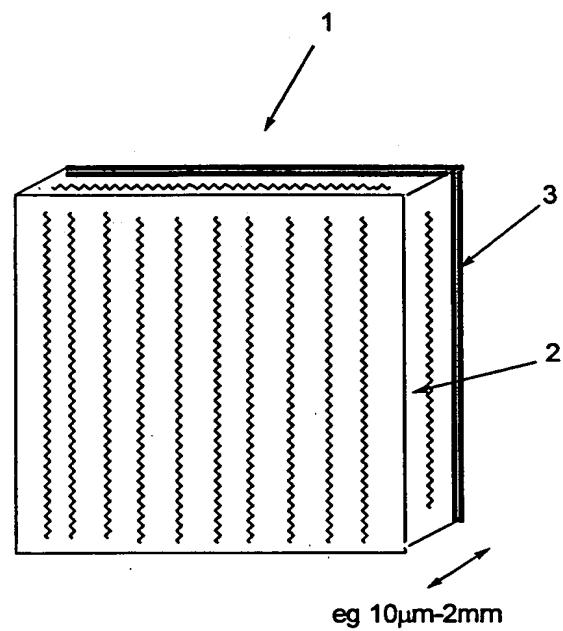
41. Use of the system according to any of claims 1-7 and method according to any of claims 8-15 for the analysis and identification of new supports for use in synthesis or separation technology.



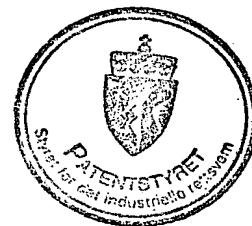
## ABSTRACT

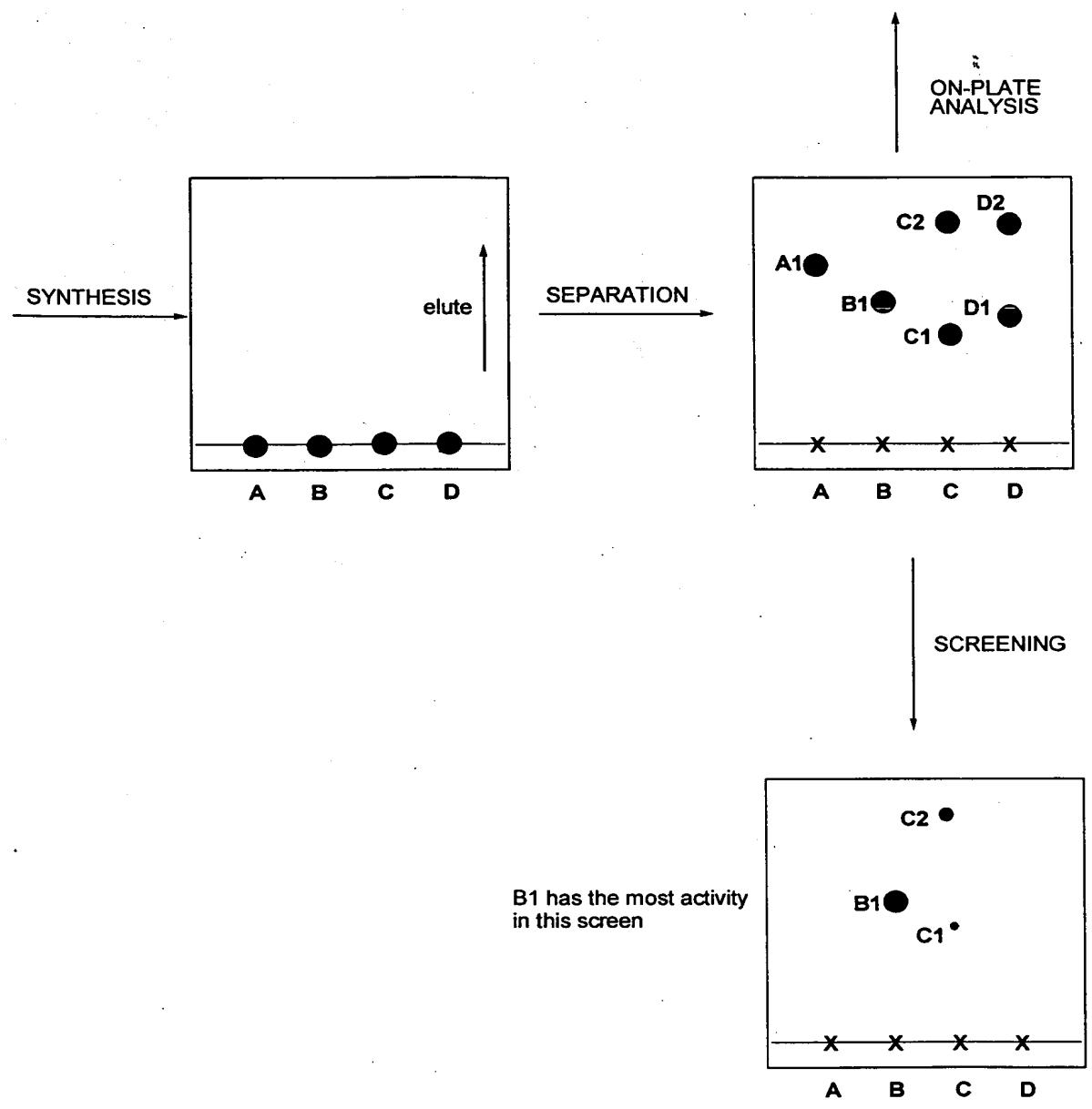
A combined technology for the synthesis, separation, screening and analysis of chemical entities, especially a combinatorial library, is described. The invention comprises a system and a method where these four processes are performed sequentially on the same medium. The technique described enables a rapid route from synthesis to the testing of chemical compounds. The chemistry does not need to be optimised and vital information can also be gained by the testing of by-products/reagents simultaneously if desired. Screens can be performed without need for reaction work-up. These 4 steps/key areas can be performed on the same medium without the need for undesired chemical manipulations, or further handling.





**Figure 1**





**Figure 2**

